

Development and NMR Validation of a Forcefield for Organophosphorus Compounds and Use in Molecular Dynamics Simulations of Nerve Agents in Solution



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Abstract:

One of the most fundamental tools in computational chemistry is molecular dynamics (MD) simulation, the use of computers to model the conformational motions of molecular systems on microsecond, nanosecond, or picosecond timescales. The simulations require the use of forcefields to provide the forms and parameters of the mathematical functions describing the potential energies of all atoms in a molecular system. Although numerous forcefields exist for proteins, nucleic acids and small molecules, not one has been developed for organophosphorus (OP) compounds such as nerve agents. We are developing such a forcefield to allow meaningful molecular mechanics and MD simulations of OP compounds in any chemical environment.

Our experimental approach centers on consistently improving and refining an initially-designed forcefield based on the existing potential energy functions in the software program, NAMD (Humphrey, W.; Dalke, A.; Schulten, K. *J. Molec. Graphics*, 1996, vol.14, pp. 33-38.), with estimated parameters for V- and G-series nerve agents and other OP compounds. The refinement process is based on comparing the nuclear Overhauser effect (NOE) build up curves measured on the nerve agents by nuclear magnetic resonance (NMR) spectroscopy to those calculated directly from MD simulations with the forcefield under development. Because NOE build up is intimately related to the distance between ¹H-¹H pairs (defined as r_{HH}), which is a direct reflection of the ensemble averaged conformation for flexible molecules such as organophosphorus (OP) compounds, accurate and realistic simulations derived from the refined forcefield should faithfully reproduce the NOE build up curves for the nerve agents at the same temperature and pressure.

NOE build up curves can be calculated directly from the MD trajectory files containing the atomic coordinates of nerve agent conformations during the course of the simulations by using r^{-6} averaging ($\langle r^{-6} \rangle$). We have identified the ¹H sites in aqueous VX that are located close enough in conformational space to generate NOE enhancements (<5 Å) and are measuring their transient NOE build up curves at different temperatures by ¹H NMR spectroscopy. Herein, we report our preliminary NMR data and initial computational chemistry efforts.

Preliminary NMR Data:

One-dimensional NOE spectroscopy was used to identify dipolar-coupled ¹H-¹H pairs in aqueous VX. An example spectrum (Figure 1) shows an irradiated signal (with negative phase) and three signals resulting from NOE enhancements (all with positive phase). Signal assignments are shown in the spectra and the accompanying VX structure (Figure 2).

Preliminary NMR Data (con't.):

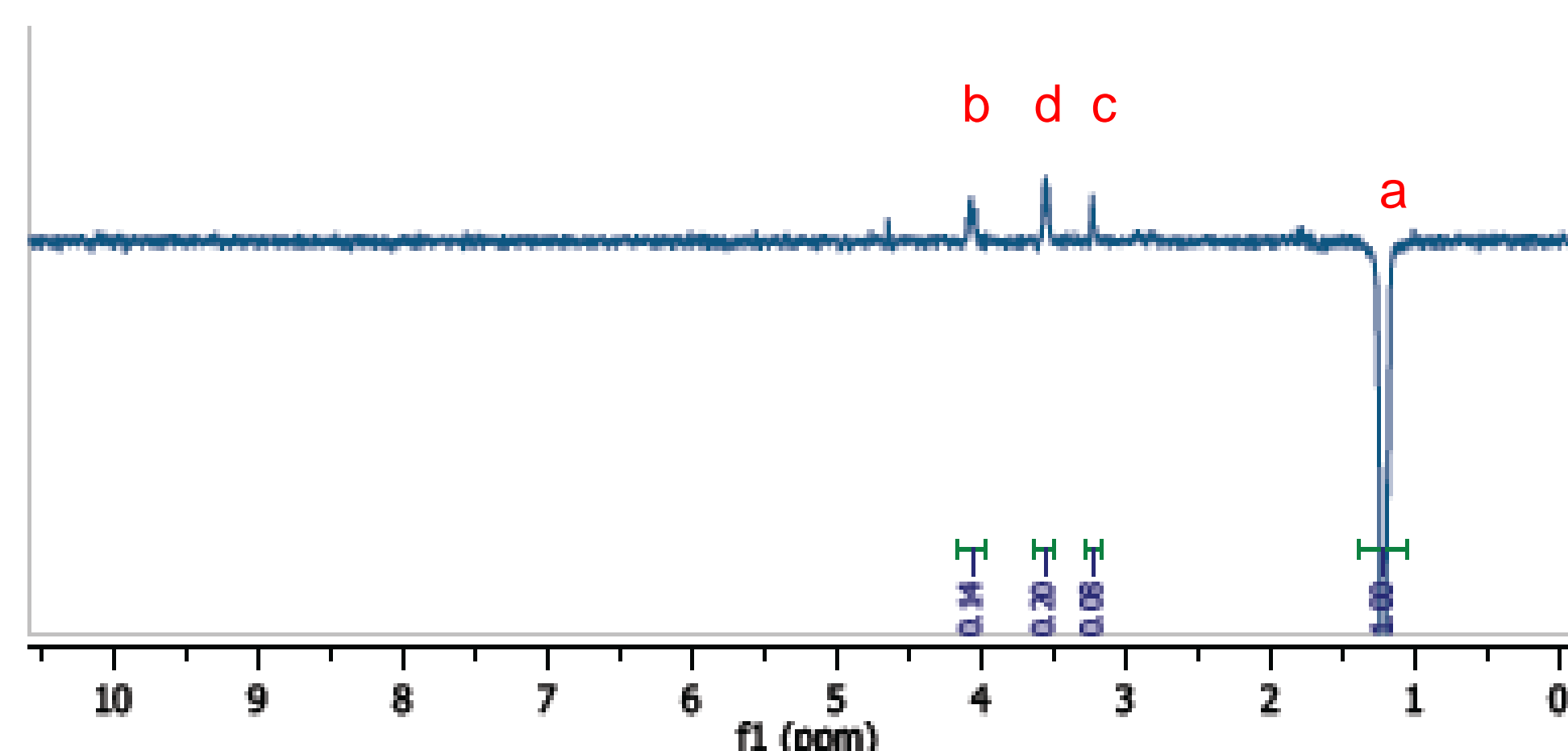


Figure 1.

We have identified the four ¹H-¹H pairs displaying the largest NOE enhancements for aqueous VX at 25 ° C (shown in Figure 2).

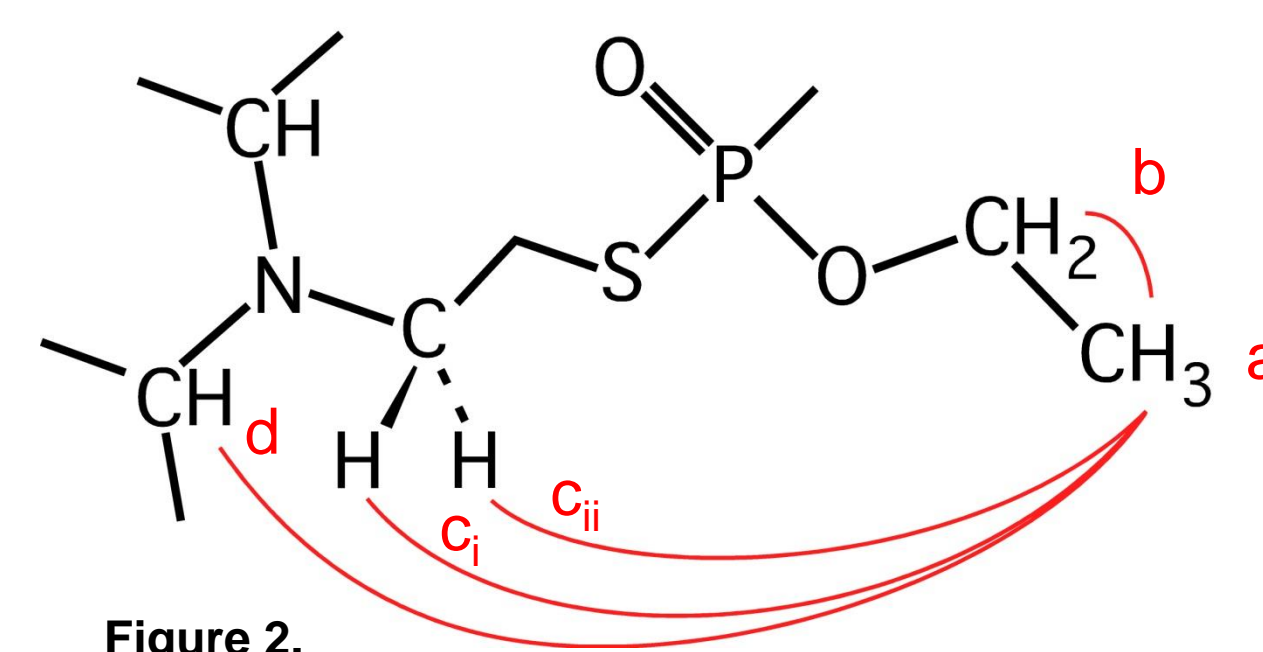


Figure 2.

The transient NOE build up for each of the four ¹H-¹H pairs was measured with the one-dimensional NOE spectroscopy technique (sample data appears in Figure 3).

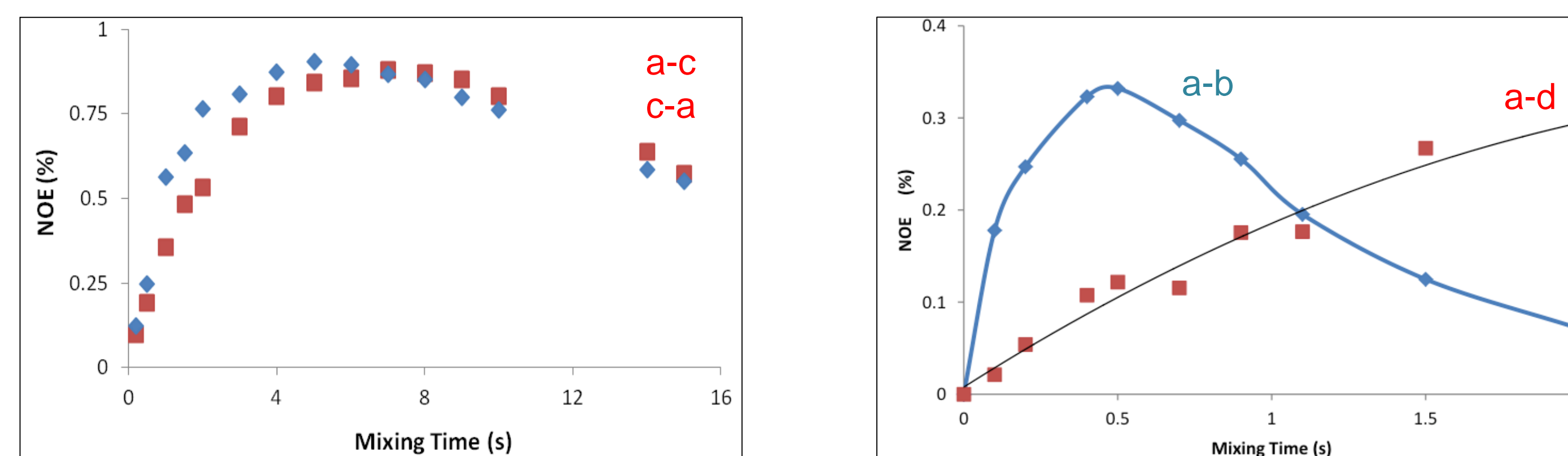


Figure 3.

Preliminary NMR Data (con't.):

Using the transient NOE build up measured for the two aromatic ¹H sites of tyrosine ($r_{HH} = 2.5$ Å), and the transient NOE data for VX, an ensemble averaged conformation was derived for the nerve agent in aqueous solution (Figure 4). The conformation reveals that the O-ethyl group folds back on the VX molecule for a significant length of time when in aqueous solution.

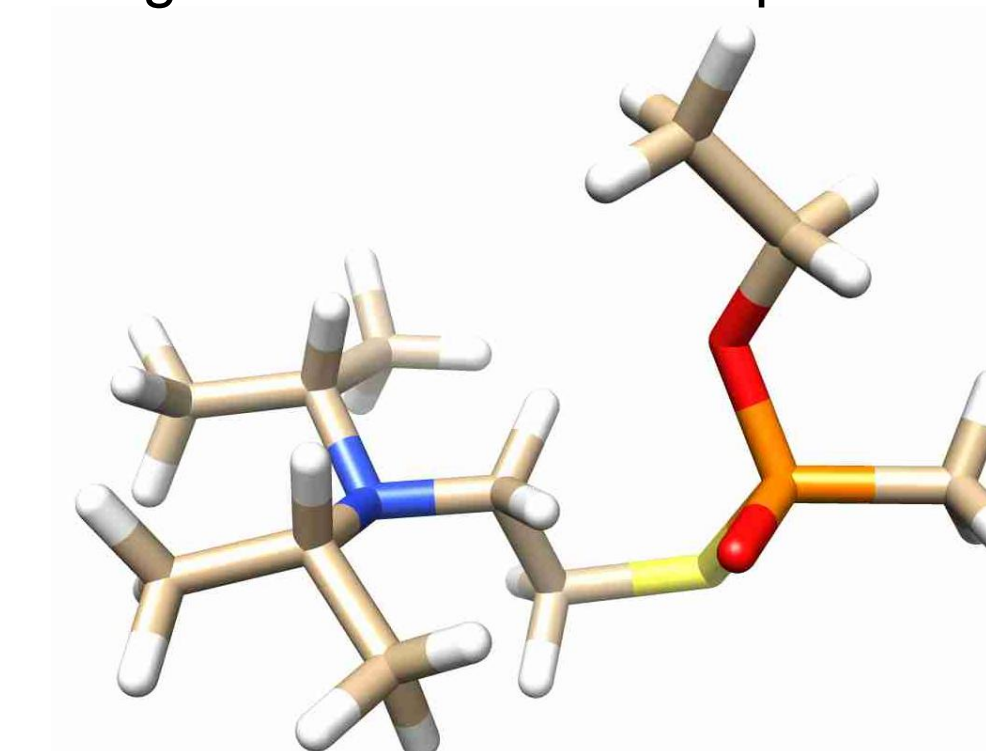


Figure 4.

Preliminary Computational Chemistry:

We have just initiated our computational efforts associated with this project. VX isomers were optimized for a minimum energy conformation as described below. Results are used to visually inspect orbitals and occupancy to construct new orbitals or select active space orbitals for CASSCF calculations and to compare differences in orbital energy and occupancy space with NMR experimentally determined distances and binding energetics.

VX molecular orbital and occupancy: MO=43, isovalue = 0.02, 36 total atoms all with neutral charge, singlet spin. Image A (left) is the surface charge with charges represented by color. The blue line is the 3.7065 debye dipole from the center of mass. Image B (right) is the isocontour at 0,0,1 in the coordinate plane. (These images were generated with the program Gaussian 09.)

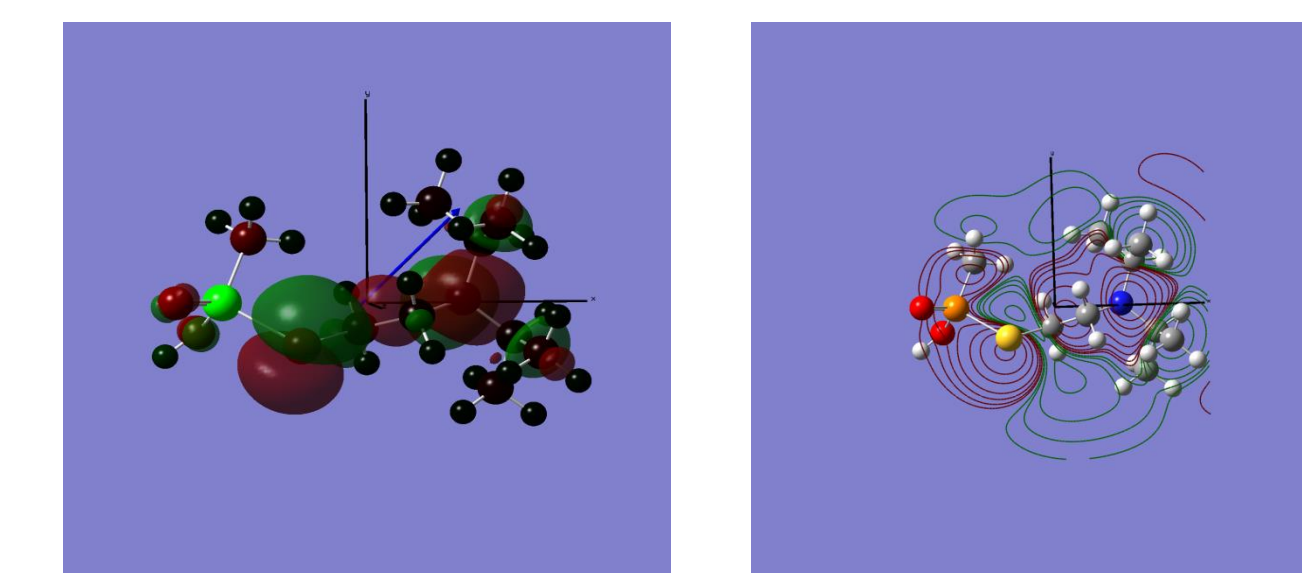


Figure 5.

Conclusions:

- Folded VX conformations have not been reported to date.
- We are currently exploring the nature of these conformations with quantum mechanical calculations and MD simulations.
- The refined forcefield will be used with NMR spectroscopy to investigate nerve agent-acetylcholinesterase (AChE) binding and the design of new non-oxime AChE reactivators.

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